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Docket No.: **F-7125**
Filing Date: **September 26, 2001**

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☐ ATTN: BOX PATENT APPLICATION
☐ ATTN: BOX DESIGN PATENT APPLICATION
☒ ATTN: BOX PCT
☒ THIS IS THE 35 U.S.C 371 NATIONAL STAGE OF **PCT/EP00/02457** FILED
March 21, 2000

Sir:

Transmitted herewith for filing is the ☒ Utility ☐ Design nonprovisional patent application
of:

Inventor / Application Identifier: **Stefan BRACHT**

☐ See Inventor Information Sheet attached

For: **TRANSDERMAL THERAPEUTIC SYSTEM WITH NICOTINE AND ADDITION OF
MONOTERPENE KETONES**

- ☐ This is a new patent application.
☒ This is the 35 U.S.C. 371 National Stage Application of the above-identified PCT Application.
☐ This is a: ☐ Continuation Application
☐ Divisional Application
☐ Continuation-in-Part Application
of prior Application Serial No. ____
☐ Cancel in this application original claims ____ of the prior application before
calculating the filing fee.
☐ Amend the specification by inserting before the first line the sentence:
-- This is a ☐ Continuation, ☐ Division, ☐ Continuation-in-part, of Application
☐ Incorporation By Reference. The entire disclosure of the prior application, from which a copy of
the oath or declaration is supplied, is considered as being part of the disclosure of the accompanying
application and is hereby incorporated by reference therein.


ENCLOSED ARE THE FOLLOWING:		
X	1	Sheets of drawings ([X] formal [] informal size A4).
X	12	Pages of specification including abstract and claims.
X	13	Total pages.
X	Combined Declaration and Power of Attorney	
	X	Newly executed
		Copy from prior application
		Inventors deleted; see attached statement
	Sequence Listing	
		Computer Readable Copy
		Paper copy
		Statement verifying identity of above copies
X	Return Receipt Postcard	
X	Preliminary Amendment	
X	Assignment to: LTS Lohmann Therapie-Systeme AG	
		Assignment is of record in prior application Serial No._.
	X	Assignment Recordation Form Cover Sheet.
	X	Charge \$40.00 to Deposit Account No. 10-1250 for recording Assignment.
X	Information Disclosure Statement	
X	Information Disclosure Citation	
	English translation	
X	Application Data Sheet	

PRIORITY CLAIMS	
	Applicant hereby claims the benefit of the filing date of the following provisional application(s) under the provision of 35 USC 119.
X	Applicant hereby claims the benefit under the provisions of 35 USC 119 of the filing dates of the following applications as indicated below: Germany Patent Appln. No. 199 13 732.3, filed March 26, 1999, Priority Claimed of which certified copies thereof
	will follow
	are enclosed
X	have been filed in the International Bureau
	were filed in prior application:

CLAIMS FILED AND FILING FEE CALCULATION					
ITEM	—			Rate	Applied Fee
[] Base Fee - Non PCT	—			\$710	
[] Base Fee - PCT IPEA-US	—			\$690	
[] Base Fee - PCT ISA-US	—			\$710	
[] Base Fee - PCT not ISA or IPEA	—			\$1,000	
[X] Base Fee - PCT with EPO or JPO Search Report	—			\$860	\$860
[] Base Fee - Design	—			\$320	
Claim Fees	Number Filed	Base Number	Number Extra over Base	—	
Total Claims	16	20	0	\$18	\$0
Independent Claims	3	3	0	\$80	\$0
Multiple Dependent Claim Fee	—			\$270	\$270
[] Small Entity Status is Asserted	—				(\$0)
[] Foreign Language Filing Fee	—			\$130	\$0
TOTAL FILING FEE					\$1,130

- [X] Please charge Deposit Account No. 10-1250 in the amount of the above TOTAL FILING FEE. A duplicate copy of this sheet is attached.
- [X] Please charge to Deposit Account No. 10-1250 any further fees due for filing or during prosecution of this application under: 37 CFR 1.16; 37 CFR 1.17; and 37 CFR 1.492.

JORDAN AND HAMBURG LLP

By 
C. Bruce Hamburg
Reg. No. 22,389
Attorney for Applicant

09/937534

JCO9 Rec'd PCT/PTO 26 SEP 2001

F-7125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Stefan BRACHT

Serial No. : Not yet known (U.S. National Stage of
PCT/EP00/02457 filed March 21, 2000)

Filed : Concurrently herewith

For : TRANSDERMAL THERAPEUTIC SYSTEM
WITH NICOTINE AND ADDITION OF
MONOTERPENE KETONES

Group Art Unit : (Not yet known)

Examiner : (Not yet known)

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to examination, please amend the above-identified patent
application as follows:

IN THE TITLE:

Please delete the title and replace it with the following:

--TRANSDERMAL THERAPEUTIC SYSTEM WITH NICOTINE AND
ADDITION OF MONOTERPENE KETONES--

F-7125

IN THE CLAIMS:

Please amend claim 5 as follows:

5, (Amended) Transdermal therapeutic system according to any one of claims 1-4, wherein the content of the at least one monoterpene ketone in the nicotine-containing matrix is 0.1 to 5.0%-wt.

The amendments to claim 5 are shown by brackets and underscoring in Appendix I.

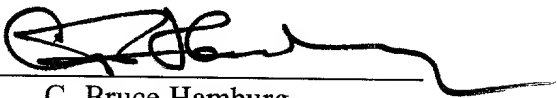
F-7125

REMARKS

This conforms the title in the specification to the title in the published PCT application and corrects an improper multiple dependency and other informalities in claim 5.

Respectfully submitted,

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CBH/pb

APPENDIX I

PENDING CLAIMS WITH AMENDMENTS EFFECTED THEREIN

5. (Amended) Transdermal therapeutic system according to any [or more] of [the preceding] claims 1-4, [characterized in that] wherein the content of the at least one monoterpene ketone[(s)] in the nicotine-containing matrix is 0.1 to 5.0%-wt.[, preferably 0.5 to 2%-wt].

1/PATS

09/937534

JC09 Rec'd PCT/PTO 26 SEP 2001

Nicotine-TTS comprising an addition of monoterpene ketones

The present invention relates to the addition of odour-improving substances to transdermal therapeutic systems (TTSs) containing nicotine. More particularly it relates to nicotine-comprising TTSs containing such additives, as well as to processes for masking the unpleasant smell of such TTSs, as well as to the use of odour-improving substances for masking the unpleasant smell of such TTSs caused by the nicotine content.

Worldwide, nicotine-containing TTSs are widely used in smoking cessation treatment. However, the systems available on the market exhibit a distinct nicotine smell, which is perceived especially when removing the systems from the package and upon application thereof.

In the course of the storage period of typically 2 to 3 years, owing to partial degradation, a marked intensification of this smell and a change up to subjectively very unpleasant types of smells can occur.

WO 95/08324 A1 describes a process for making TTSs of at least two layers, using a highly volatile ingredient as exclusive solvent. These TTSs may contain various active agents, including nicotine as well as, inter alia, menthol or other volatile terpene derivatives, as skin penetration enhancer. No special action of these additives with respect to smell in nicotine-comprising TTSs has been described. As regards the "volatile terpene derivatives" no differentiation is made between monoterpene alcohols and monoterpene ketones.

EP 0 356 382 A2 discloses TTSs based on certain block copolymers, wherein also nicotine may be used as an active

agent. To improve skin penetration, eucalyptol or eucalyptus oils are proposed, putting special emphasis on cineol as main component; ingredients of mint oils are not considered. The aspect of the unpleasant smell of nicotine-comprising patches has likewise not been considered.

US 5 599 554 A concerns the transmucosal or transdermal application of nicotine, wherein the compositions employed may also contain odoriferous substances or flavours. The characteristic smell of nicotine is mentioned, it is true, but it is not described as being of disadvantage. Aromatic compounds such as menthol or eucalyptol, but not essential mint oils or terpene ketones, are mentioned as optional ingredients. No indication is made of the function of those additives. Presumably, they serve to improve taste in oral administration forms.

US 5 593 684 A describes a method for treatment based on the simultaneous transmucosal and transdermal administration of nicotine. Here, terpene-containing plant secretions are employed as "etherial oils" in lozenges for oral application in order to mask the unpleasant taste of nicotine.

US 4 933 184 concerns TTSSs with improved transdermal active substance delivery, inter alia for nicotine, with menthol being utilized as enhancer; no mention is made of other substances occurring in etherial oils of mint species, e.g. monoterpene ketone. A mint oil was examined as enhancer, as an alternative to menthol, but surprisingly did not yield that effect. As for the rest, this publication merely relates to the improvement of active substance permeation, not to a process for improving the smell of TTSSs.

It is thus the object of the present invention in nicotine-containing TTSSs according to the introductory part of Claim

1, to neutralise this characteristic smell, or mask it with a more pleasant smell, by adding suitable odoriferous substances.

The solution of this task has now been found in the addition of essential oils of various mint species or of components thereof, especially of monoterpene ketones. In accordance with the invention, these additives can be used to mask or improve the unpleasant smell of nicotine-comprising TTSs. The TTSs according to the invention have a content of at least one essential oil extracted from a mint species, or of a monoterpene ketone occurring in these essential oils.

The components of the essential oils of various mint species are dominated by products of the terpene metabolism, more precisely by monoterpenes.

Mint oils are generally characterized by their pleasant, refreshing smell. Examples of oils used are peppermint oil, spearmint oil or poleimin oil, each extracted from different plants.

The characteristic monoterpenes contained in these oils can be subdivided into monoterpene alcohols and monoterpene ketones.

Typical monoterpene alcohols are: menthol, isomenthol, neomenthol, neoisomenthol and isopulegol.

Typical monoterpene ketones are: menthone, isomenthone, carvone, piperitone, pulegone and isopulegone.

Practically all of these representatives exist as enantiomers both in an optically levorotatory and a dextrorotatory form.

As representatives of this group the essential oils of peppermint (*Oleum Menthae peperitae*), spearmint (*Oleum*

Menthae crispae) and (Japanese) mint (*Oleum Menthae arvensis*) were examined.

Peppermint oil and especially mint oil are dominated by monoterpene alcohols, especially menthol. Spearmint oil, by contrast, contains above all monoterpene ketones, especially carvone (cf. monograph "Pfefferminzöl" [Peppermint oil] in the European Pharmacopeia 1997; monograph "Minzöl" [Mint Oil] in the German Pharmacopeia 1997; as well as G. Schneider: *Pharmazeutische Biologie* [Pharmaceutical Biology], 2nd ed. 1988, BI Wissenschaftsverlag, S. 342-345).

As single substances, (-)-menthol and (-)-menthone were tested as typical monoterpene alcohol and typical monoterpene ketone, respectively.

Examples:

To examine the effect of such additives, a simplified smelling-test model was devised.

Nicotine was mixed in a concentration of 7%-wt. with miglyol 812. Miglyol 812 is a saturated triglyceride serving as an odourless carrier. The concentration of 7%-wt. of nicotine corresponds approximately to the active substance concentration used in TTSS of 5-10%-wt. For nicotine in miglyol, a vapour pressure comparable to that of TTSS, and thus a similar intensity of smell, results. To this test mixture were added 5 test substances or test mixtures:

(-)-Menthol, (-)-menthone, peppermint oil (quality according to European Pharmacopeia), spearmint oil (quality according to Deutscher Arzneimittel Codex DAC [German Codex of Pharmaceuticals] and mint oil (quality according to German Pharmacopeia).

The quantities added amounted to 0.5, 1.0 and 2.0%-wt. in each case.

This yielded 15 test samples. In addition, one sample was prepared without odour-improving additive.

These 16 sample were assessed by 6 subjects as to odour, with the kind and amount of the respective additive not being known to the subjects.

The assessment criteria and rating numerals comprise:

1. Nicotine smell: imperceptible (4); faint (3);
 moderate (2); distinct (1)
2. Overall impression: unpleasant (1); neutral (2);
 pleasant (3); fragrant (4)

The assessment of the overall impression was multiplied by the factor 2, for greater emphasis as against the nicotine smell, before adding the two values for each sample and person. Higher values signify a more favourable assessment. The rating numerals were used to form the mean value. The theoretical minimal value is 3.0 and the theoretical maximum value is 12.0.

The results are shown in Table 1:

Test produkt/Amount	0,5%-wt.	1,0%-wt.	2,0%-wt.
(-)-Menthol	4,0	4,1	4,9
(-)-Menthone	6,6	6,4	8,6
Peppermint oil	6,9	8,7	9,3
Spearmint oil	7,3	7,7	9,6
Mint oil	6,0	7,0	9,0

The product without additive yielded the value 4.0.

A graphic representation of the results is shown in FIG. 1.

This shows a very surprisingly clear advantage of menthone over menthol. The less favourable results of mint oil, which is dominated by menthol (G. Schneider; Pharmazeutische Biologie, 2nd ed. 1988, BI Wissenschaftsverlag, p. 345) as compared to peppermint oil, typically containing up to 32% of menthone (European Pharmacopeia 1997), is supportive of these findings.

Finally, spearmint oil, which is dominated by carvone and is practically free from menthol, yielded the best results.

Overall, this demonstrates a clear advantage of monoterpene ketones, or mixtures of monoterpene alcohols and monoterpene ketones, over pure monoterpene alcohols.

The practical realisation of adding the substances according to the invention to nicotine-containing TTSS meets with certain difficulties because of the high volatility of the substances; however, these difficulties can be eliminated by observing the teaching of PCT/WO 95/08324.

The quantity of monoterpene ketone(s) or of essential oil contained in the nicotine-comprising matrix of the odour-improved TTSS according to the invention amounts to 0.1 to 5.0%-wt., preferably 0.5 to 2%-wt.

Thus, the addition of substances according to the present invention to nicotine-containing TTSS constitutes a useful means for improving the unpleasant smell of such TTSS.

The TTSS possessing the features as described in the introductory part of Claim 1 are characterized, as mentioned above, by a content of at least one essential oil extracted from a mint species, or a monoterpene ketone occurring in these essential oils.

Preferably the monoterpene ketone is one from the group of carvone, dihydrocarvone, menthone, isopulegone, isomenthone, neomenthone, neoisomenthone or piperitone. The monoterpene ketones may be utilized as pure enantiomers or mixtures thereof.

As essential oil, peppermint oil (*Oleum Menthae crispae*) is used with particular preference.

The content of monoterpene ketone(s) or of essential oils in the nicotine-containing matrix is preferably 0.1 to 5.0%-wt., especially preferred 0.5 to 2%-wt.

The invention further relates to a process for masking an unpleasant smell, caused by a content of nicotine, of a transdermal therapeutic system, this process being characterized in that at least one odour-improving substance is added to the nicotine-containing transdermal therapeutic system, said substance being an essential oil extracted from a mint species, or being a monoterpene ketone contained in an essential oil extracted from a mint species.

Here, preferably, the monoterpene ketones mentioned above or peppermint oil may be used as monoterpene ketones or essential oil, respectively, it being possible to utilize the monoterpene ketones as pure enantiomers or as mixtures thereof.

The monoterpene ketone(s) or the essential oil(s) of the nicotine-containing matrix are preferably used in a concentration of 0.1 to 5.0%-wt, especially preferred in a concentration of 0.5 to 2%-wt.

Further, the invention comprises the use of an essential oil extracted from a mint species and/or of a monoterpene ketone contained in an essential oil extracted from a mint species, for masking an unpleasant smell of a transdermal

therapeutic system, said smell being caused by a content of nicotine in said transdermal therapeutic system.

Preferably, the monoterpene ketone used is one from the group of carvone, dihydrocarvone, menthone, isopulegone, isomenthone, neomenthone, neoisomenthone or piperitone, it being possible to use the monoterpene ketones as pure enantiomers or as mixtures thereof.

As essential oil, peppermint oil (*Oleum Menthae crispae*) is used with particular preference.

In the use according to the invention for masking an unpleasant smell of a nicotine-containing transdermal therapeutic system, the monoterpene ketone(s) or the essential oil are/is added to the nicotine-containing matrix preferably in a concentration of 0.1 to 5.0%-wt, particularly preferred in a concentration of 0.5 to 2%-wt.

CLAIMS

1. Transdermal therapeutic system having a backing layer, at least one nicotine-containing layer or zone, which may have pressure-sensitive adhesive properties, as well as a removable protective layer, characterized by a content of at least one essential oil extracted from a mint species, or at least one monoterpene ketone contained in these essential oils.
2. Transdermal therapeutic system according to claim 1, characterized in that the monoterpene ketone is one from the group of carvone, dihydrocarvone, menthone, isopulegone, isomenthone, neomenthone, neoisomenthone or piperitone.
3. Transdermal therapeutic system according to claim 2, characterized in that the monoterpene ketones are used as pure enantiomers or mixtures thereof.
4. Transdermal therapeutic system according to claim 1, characterized in that the essential oil is spearmint oil (*Oleum Menthae crispae*).
5. Transdermal therapeutic system according to one or more of the preceding claims, characterized in that the content of monoterpene ketone(s) in the nicotine-containing matrix is 0.1 to 5.0%-wt., preferably 0.5 to 2%-wt.
6. Process for masking an unpleasant smell, caused by a content of nicotine, of a transdermal therapeutic system, characterized in that at least one odour-improving substance is added to the nicotine-containing transdermal therapeutic system, said substance being an essential oil extracted from a mint species, or being a monoterpene

ketone contained in an essential oil extracted from a mint species.

7. Process according to claim 6, characterized in that the essential oil is peppermint oil (*Oleum Menthae crispae*).

8. Process according to claim 6, characterized in that the monoterpene ketone is one from the group of carvone, dihydrocarvone, menthone, isopulegone, isomenthone, neomenthone, neoisomenthone or piperitone.

9. Process according to claim 8, characterized in that the monoterpene ketone(s) are added to the nicotine-containing matrix preferably in a concentration of 0.1 to 5.0%-wt, particularly preferred in a concentration of 0.5 to 2%-wt..

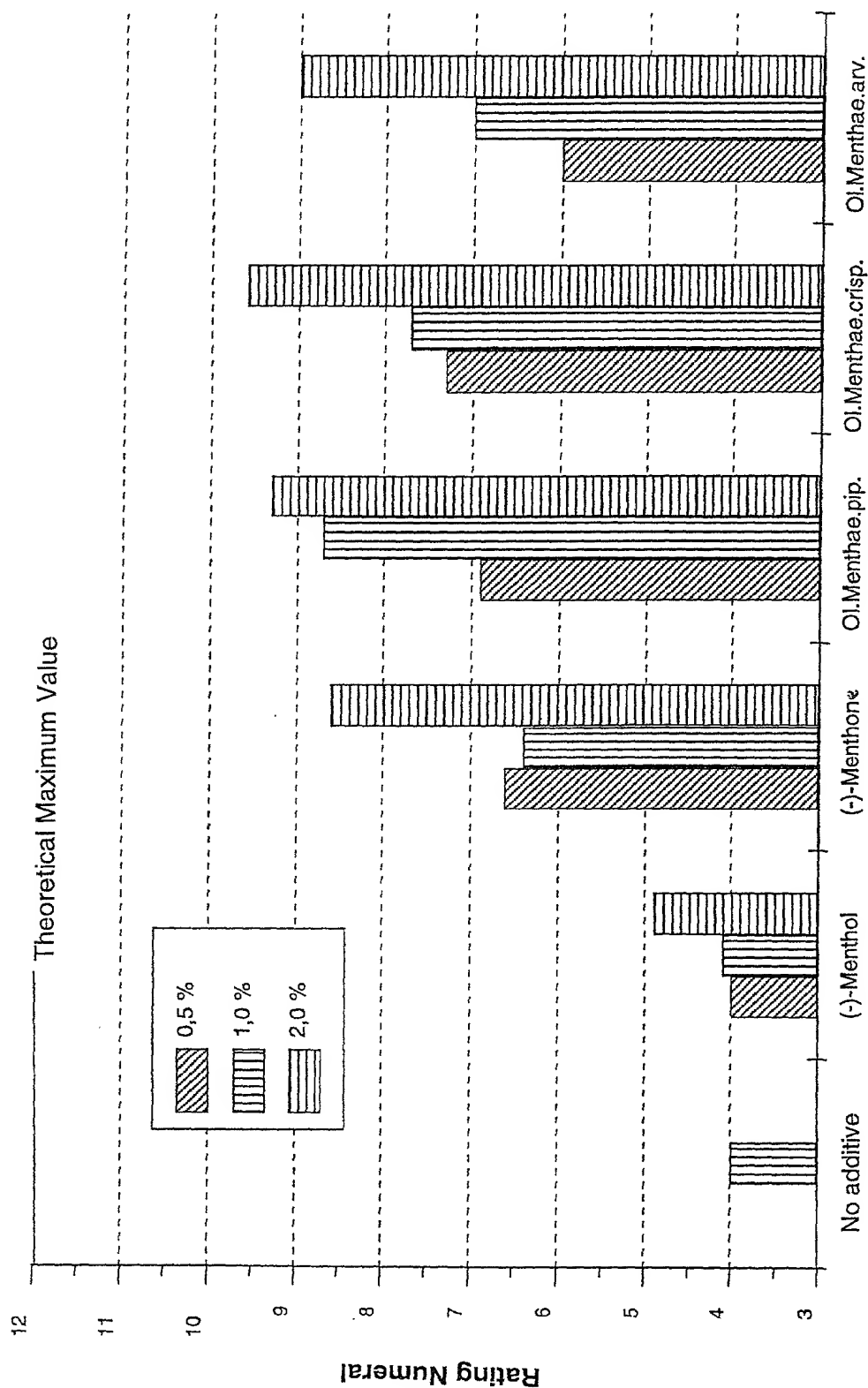
10. Use of an essential oil extracted from a mint species and/or of a monoterpene ketone contained in an essential oil extracted from a mint species, for masking an unpleasant smell of a transdermal therapeutic system, said smell being caused by a content of nicotine in said transdermal therapeutic system.

11. Use according to claim 10, characterized in that the monoterpene ketone is one from the group of carvone, dihydrocarvone, menthone, isopulegone, isomenthone, neomenthone, neoisomenthone or piperitone

12. Use according to claim 11, characterized in that the monoterpene ketone(s) are added to the nicotine-containing matrix preferably in a concentration of 0.1 to 5.0%-wt, particularly preferred in a concentration of 0.5 to 2%-wt.

13. Use according to claim 10, characterized in that the essential oil is peppermint oil (*Oleum Menthae crispae*).

FIG. 1



LTS 1999/02457
199 13 732.3

**COMBINED DECLARATION FOR PATENT APPLICATION AND
POWER OF ATTORNEY**

(Includes Reference to PCT International Applications)

Attorney's Docket Number

F- 7125

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**TRANSDERMAL THERAPEUTIC SYSTEM WITH NICOTINE AND ADDITION OF
MONOTERPENE KETONES**

the specification of which (check only one item below):

- ☐ is attached hereto.
☐ was filed as United States application
Serial No. _____,
on _____,
and was amended
on _____ (if applicable).
☒ was filed as PCT international application
Number PCT/EP00/02457,
on March 21, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:			
Country (if PCT indicate "PCT")	Application Number	Date of Filing (day, month, year)	Priority Claimed Under 35 USC 119
Germany	199 13 732.3	26 March 1999	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

**COMBINED DECLARATION FOR PATENT APPLICATION AND
POWER OF ATTORNEY (Continued)**
(Includes Reference to PCT International Applications)

Attorney's Docket Number

F-7125

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120.					
U.S. APPLICATIONS			STATUS (Check One)		
U.S. Application Number	U. S. Filing Date		Patented	Pending	Abandoned
PCT APPLICATIONS DESIGNATING THE U.S.					
PCT Application No.	PCT Filing Date	U.S. Serial Numbers Assigned (if any)			

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Full Name of Sole or First Inventor <u>Stefan BRACHT</u>	Inventor's Signature <u>X</u> <i>Stefan Bracht</i>	Date <u>X</u> <u>08/28/01</u>
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Full Name of Second Joint Inventor, if any	Inventor's Signature	Date
Residence		Citizenship
Post Office Address		